FORM PTO-1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: GEI-073

U.S APPLICATION NO (If known, see 37 C F R 1.5): 09/423109

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR99/02588	October 25, 1999	

TITLE OF INVENTION: NEW HORMONAL COMPOSITION AND ITS USE

APPLICANT(S) FOR DO/EO/US: JACQUES PARIS et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1) .
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☐ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    Also Submitted: Form PCT/RO125 November 1993 (1 page)

514 Rec'd PCT/PTO 29 OCT 1999

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/423109	PCT/FR99/02588	GEI-073

17. The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO..... $830.00	$970.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $640.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))..$710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO..... $950.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... $90.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate	
Total claims	17 -20 =	0	X $22.00	$
Independent Claims	01 -3 =	0	X $74.00	$
Multiple dependent claims(s) (if applicable)		0	+ $230.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 970.00
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				$ 970.00
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 970.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$
TOTAL FEES ENCLOSED =				$ 970.00
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of $ 970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Bierman, Muserlian and Lucas
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New York, N.Y. 10016

Charles A. Muserlian
SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Form PTO-1390 (REV 5-93)

GEI-073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: : PCT Date: 10/25/99
JACQUES PARIS et al :
PCT No.: PCT/FR99/02588 :
Filed: Concurrently Herewith :
For: NEW HORMONAL...AND ITS US :

600 Third Avenue
New York N.Y. 10016
October 29, 1999

PRELIMINARY AMENDMENT

Asst. Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

Page 2, line 9 from the bottom, change "consecutive treatments" to --sequential treatments--

IN THE CLAIMS:

Claim 12, line 1, cancel "Claims 10 and 11" and insert --Claim 10--

Claim 13, line 1, cancel "Claims 10 to 12" and insert --Claim 10--

REMARKS

The present amendment is being made in order to conform the claim dependency to the American patent practice.

Respectfully submitted,
Bierman, Muserlian and Lucas

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CAM:ds
Enclosures

NEW HORMONAL COMPOSITION AND ITS USE

Laboratoire THERAMEX

SUMMARY OF THE TECHNICAL CONTENT OF THE INVENTION

The present invention relates to the field of therapeutic chemistry and more particularly to the field of pharmaceutical hormonal technique.

More precisely, its subjects are new pharmaceutical hormonal compositions formed of an estrogen-progestative association consisting of an estrogen compound and a progestative compound, in combination or admixed with one or more non-toxic, inert pharmaceutically-acceptable diluents suitable for oral administration.

The present invention also concerns the use of the estrogen-progestative mixture in which the estrogen compound and the progestative compound are administered in combination. The combined association may be prescribed continuously or discontinuously, with a view to produce a composition designed to treat estrogen deficiencies and to prevent osteoporosis and cardiovascular disorders in menopausal women.

A further object of the invention is a process for the preparation of the said new pharmaceutical estrogen-progestative compositions.

NEW HORMONE COMPOSITION AND ITS USE

The present invention relates to the field of therapeutic chemistry and more particularly to the field of pharmaceutical hormonal technique.

More precisely, its subjects are new pharmaceutical compositions formed of an estrogen-progestative association designed to correct estrogen deficiencies in women, regardless of their origin, and more particularly in menopausal women.

In particular its objective is an estrogen-progestative association characterised in that it consists of dose units containing a combination of a progestative and an estrogen, both compounds being present at the same time in each medicinal dose.

Specifically, its subjects are new pharmaceutical compositions intended for hormone replacement therapy in menopause, which contain as active ingredient a progestational agent chosen from among nomegestrol and its esters and an estrogen agent chosen from among estradiol and its esters and the conjugated equine estrogens.

This association is intended for administration via the oral route, be it continuously or discontinuously.

As is known, over the course of less than a century the life expectancy of women has increased from 50 to 80 years, while the mean age at which the menopause begins has remained unchanged. Thus, women spend almost one-third of their life in a condition of estrogen deficiency, and this results in a higher risk of osteoporosis and cardiovascular disorders. Replacement therapy for the menopause has therefore become very widespread. It is administered either orally or, at least as regards its estrogen component, via the percutaneous route. Nevertheless, compliance seems better when the treatment is administered orally (ETTINGER et al., 1998).

Consecutive replacement therapy in the menopause cures the symptomatology of the climacteric.

It prevents osteoporosis and the onset of cardiovascular disorders. It creates artificial cycles which are followed by deprivational bleeding. This therapeutic scheme is particularly well suited to women whose menopause is recent, but it is not always well accepted in the long term, which partly explains the poor compliance with the treatment (DRAPIER FAURE E., Gynecology, 1992, 43: 271-280).

To overcome this drawback combined associations have been developed in which the two components are taken simultaneously, whether continuously or discontinuously, the effect of the progestative being to permanently oppose the proliferative action of the estrogen upon the endometrium, so inducing an atrophy of the endometrium and consequently preventing deprivation bleeding (HARGROVE J.T., MAXSON W.S., WENTZ A.C., BURNETT L.S., Obstet. Gynecol., 1989, 73: 606-612). In fact, under these conditions the endometrial atrophy is pronounced (WOLFE and PLUNKETT, 1994; PIEGSA et al., 1997; AFFINITO et al., 1998), there is no endometrial hyperplasia (STADBERG et al., 1996) and the frequency of bleeding is low and decreases with time (PIESGA et al., 1997; CARRANZA-LIRA, 1998; ETTINGER et al., 1998). With this type of treatment, compliance is generally good (EIKEN and KULTHOFF, 1995; DOREN et al., 1996), and certainly better than with consecutive treatment (EIKEN et al., 1996). The quality of life too seems improved (ULRICH et al., 1997). It is also known that this type of treatment protects the bone mass (EIKEN et al., 1996; EIKEN et al., 1997; HART et al., 1998; RECKER et al., 1999).

This "no-periods" scheme is particularly well suited for women whose menopause occurred already some time ago. Consecutive associations can be prescribed subsequently in order to improve long-term compliance with hormone replacement therapy in the menopause.

During consecutive treatments the progestative dose chosen is that which, in the long term, leads to at least 1% of endometrial hyperplasia when the progestative is administered discontinuously for more than 10 days per cycle in menopausal women undergoing estrogen replacement therapy (WHITEHEAD et al., J. Reprod. Med., 1982, 27: 539-548; PATERSON et al., Br. Med. J., 1980, 22 March: 822-824).

The progestative dose to be used in a combined replacement therapy is generally lower than that normally prescribed in consecutive schemes. Examples are micronised progesterone, dydrogesterone (FOX H., BAAK J., VAN DE WEIJER P., AL-AZZAWI E., PATERSON M., JOHNSON A., MICHELL G., BARLOW D., FRANCIS R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 119) and medroxyprogesterone acetate (BOCANERA R., BEN J., COFONE M., GUINLE I., MAILAND D., SOSA M., POUDES G., ROBERTI A., BISO T., EZPELETA D., PUCHE R., TOZZINI R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 40), which have been used respectively at doses of 100, 10 and 5 mg/day with encouraging results at the clinical and endometrial level.

Combined treatment is most often used continuously i.e. without interruption. Some, however, prefer to use it intermittently, for example on 25 days each month (BIRKAUSER M., et al.; Hormone substitution: a well defined indication and individual treatment schemes are decisive for the success of the therapy, Med. & Hyg., 1995, 53: 1770-1773). The purpose of interrupting the treatment is to remove the inhibition by the progestative of the synthesis of estradiol and progesterone receptors and so to avoid reducing the receptivity of the hormone-dependent tissues.

The progestative used according to the present invention is nomegestrol or one of its esters, mainly nomegestrol acetate. Nomegestrol acetate is a powerful progestative which is active via the oral route and has an original pharmacological profile:

- in contrast to the derivatives of 19-nortestosterone, nomegestrol acetate shows no residual androgenic and estrogenic action;
- in common with the derivatives of 17-alpha-hydroxyprogesterone it has a pure pharmacological profile, but in contrast to them it has a powerful antigonadotropic action.

It belongs to the category of qualified hybrid progestatives (OETTEL et al., 1999), which have no harmful metabolic effects because of the absence of a 17-alpha-ethinyl function, and which combine the advantages of the progesterone derivatives with those of the most modern among the 19-nortestosterone derivatives.

Its use in consecutive administration during the menopause at a dose of 5 mg/day for 12 days per cycle, in association with various types of estrogens, makes it possible to prevent endometrial hyperplasia as has been shown by a multicentric trial in 150 women over 1 year (THOMAS J.L., BERNARD A.M., DENIS C., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr. 372).

The absence of hyperplasia was confirmed in a study in which nomegestrol acetate was administered at the same dose for 14 days per cycle to women being treated with percutaneous estradiol (BERNARD A.M. et al., Comparative evaluation of two percutaneous estradiol gels in combination with nomegestrol acetate in hormone replacement therapy. XIV World Congress of Gynecology and Obstetrics, FIGO, Montreal, 24-30 September 1994). This utilisation, which is covered by French Patent No. 2.737.411 in the name of the Applicant Company, claims a dose range from 1.5 to 6 mg and preferably from 2.5 to 5 mg.

The estrogen used is estradiol, free or esterified, and in particular estradiol valerate, or the conjugated equine estrogens, presented in a formulation that is active via the oral route. It has been shown that an estradiol dose of between 1 and 2 mg/day is enough to combat the estrogen deficiency in menopausal women.

The nomegestrol acetate and free or esterified estradiol, or the conjugated equine estrogens are administered in one of the forms that is suitable for oral administration : gelatine capsules, capsules, pills, powder sachets, tablets, coated tablets, sweetened tablets, etc.

The present invention is characterised by the fact that it is a new estrogen-progestative association which is active via the oral route, and is administered in combination. A further object of this invention is the use of compositions according to the invention to correct estrogen deficiencies and to prevent osteoporosis and cardiovascular disorders in menopausal women.

The present invention is also defined by :

a) The fact that the estrogen-progestative association concerned is different from those described before now for the same type of indications.

Certain patents claim the continuous use of estrogen-progestative combinations for replacement therapy in menopause. Examples are the patents US 5108995 or EP 309263. It is evident, however, that these patents claim multisequential treatments with dose changes of the active ingredients. This is also true of the patents filed in the USA (US 4820831 A) and in Europe (EP 136 011) in the name of PLUNKETT. Those patents claim the use of numerous estrogens and numerous progestatives in menopause replacement therapy. It seems, however, that the said claims do not cover the use of all progestatives, on the one hand for scientific reasons and on the other hand for scientific and legal reasons related to the wording of the claims of the two said patents:

1) The use of numerous progestatives is based on equivalences with one of them, in this case levonorgestrel. This approach seems unacceptable because different progestatives have very different pharmacological profiles and the doses to be used cannot be deduced from a simple and unique equivalence system, as becomes clear from the active dose ranges proposed for different progestatives in 3 different patents (Table 1).

It can be seen that the lower limit for the various progestatives varies in a ratio of 2.4 to 50 while the maximum dose varies in a ratio of 1 to 50. Thus, for indications of the same type, the dose range varies very considerably from one patent to the next and this shows that the system of equivalence does not lend credibility to the relationship which could be established between progestatives.

2) Apart from the above, it would be reasonable to think that the doses claimed should be based on data from clinical pharmacology and/or clinical data previously published and commonly accepted. Now, if the doses defined as in the PLUNKETT patents are considered, it is easy to see that in most cases the active doses published already a long time ago, i.e. before the said patents were filed (NEUMANN, 1977) or more recently (KUHL, 1996), are very coherent but only rarely lie within the dose ranges claimed in the patents in the name of PLUNKETT (Table 2).

This finding is also valid if, instead of the active doses as above, account is taken of the active dose ratios given by taking norgestrel as reference (= 1) (Table 3).

Table No. 1 Doses (µg/day) of the various progestatives claimed according to the patents

PROGESTATIVE	PATENT	DOSE (µg/day)	
		Minimum	Maximum
Levonorgestrel	WO 95/17194	60	125
Levonorgestrel	EP 025607 A1	25	100
Levonorgestrel	PLUNKETT	25	75
Gestodene	WO 95/17194	50	75
Gestodene	EP 025607 A1	10	70
Desogestrel	WO 95/17194	60	150
Desogestrel	EP 025607 A1	25	100
3-ketodesogestrel	WO 95/17194	60	150
3-ketodesogestrel	EP 025607 A1	25	100
Norethisterone	WP 95/17194	350	750
Norethisterone	EP 025607 A1	85	350
Norethisterone	PLUNKETT	150	1 000
Norethisterone acetate	PLUNKETT	100	1 000
Norgestimate	WO 95/17194	200	300
Norgestrel	PLUNKETT	50	150
Ethynodiol diacetate	PLUNKETT	100	1 000
Dihydrogesterone	PLUNKETT	5 000	30 000
MPA	PLUNKETT	1 000	15 000
Norethynodrel	PLUNKETT	200	5 000
Allylestrenol	PLUNKETT	1 000	10 000
Lynoestrenol	PLUNKETT	100	2 000
Quingestanol acetate	PLUNKETT	50	1 000
Medrogestone	PLUNKETT	1 000	10 000
Norgestrienone	PLUNKETT	20	200
Dimethisterone	PLUNKETT	500	15 000
Ethisterone	PLUNKETT	1 000	25 000
Cyproterone acetate	PLUNKETT	100	10 000
Cyproterone acetate	WO 95/17194	100	200

Table No. 2
Doses of each progestative according to the various bibliographical references

	US Pat. 4826831		NEUMANN PUBLICATION				KUHL	
	Min.	Max.	Endometrium (1)	Menstruation (2)	Ovulation (3)	Contraception (4)	Endometrium (1)	Ovulation (3)
Levonorgestrel	25	75					**400**	60
Norgestrel	50	150	**1200**	**2000**	100	**250**		
Norethisterone	150	1000	**12500**	**5000**	800	1000	**10000**	400
Norethisterone acetate	100	1000	**4500**		800	1000		
Ethynodiol diacetate	100	1000						
Dydrogesterone	5000	30000				5000		
MPA	1000	15000	5500	**25000**				
Norethynodrel	200	5000	**10000**	**7500**	6000	2500		
Allylestrenol	1000	10000	1750					
Lynoestrenol	100	2000	**5000**			**2500**		
Quingestanol acetate	50	1000						
Medrogestone	1000	10000						
Norgestrienone	20	200						
Dimethisterone	500	15000						
Ethisterone	1000	25000						
CIP acetate	100	10000	1000		1000	2000	2000	1000

The cases appearing **in bold** above correspond to active doses outside the dose ranges claimed in the "PLUNKETT" patents. The doses (**µg/day**) are those necessary to induce transformation of the endometrium (1), to produce an adequate delay in the onset of periods (2), to inhibit ovulation (3), or to have a contraceptive effect (4).

Table No. 3: Dose ratios of each progestative according to the various bibliographical references
The reference progestative is norgestrel (= 1)

	US Pat. 4826831		NEUMANN			
	Ratios		Ratios			
	Min.	Max.	Endometrium (1)	Ovulation (3)	Menstruation (2)	Contraception (4)
Levonorgestrel	0.5	0.5				
Norgestrel	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**	**1.0**
Norethisterone	3.0	6.7	***10.4***	***8.0***	***2.5***	4.0
Norethisterone acetate	2.0	6.7	3.8	***8.0***		4.0
Ethynodiol diacetate	2.0	6.7				
Dydrogesterone	100.0	200.0				
MPA	20.0	100.0	***4.6***		***12.5***	20.0
Norethynodrel	4.0	33.3	8.3	***60.0***	***3.8***	10.0
Allylestrenol	20.0	66.7	***1.5***			
Lynoestrenol	2.0	13.3	4.2			10.0
Quingestanol acetate	1.0	6.7				
Medrogestone	20.0	66.7				
Norgestrienone	0.4	1.3				
Dimethisterone	10.0	100.0				
Ethisterone	20.0	166.7				
CIP acetate	2.0	66.7	***0.8***	10.0		8.0

The cases appearing ***in bold and Italics*** correspond to active doses outside the ratio ranges claimed in the US and EP patents cited in the name of PLUNKETT. For the meanings of (1), (2), (3) and (4), see Table 2.

Reasoning related to the claims

1) In the US patent cited above, Claims 1 and 2 relate to continuous treatments ; the only progestatives claimed are dl-norgestrel and levonorgestrel. The subsequent claims concern discontinuous multisequential treatment, i.e. a therapeutic scheme different from that proposed in the present patent application. For this latter type of therapeutic regime the number of progestatives claimed is larger but the list thereof is precise and limited, as emerges from the Markush-type presentation of the said claims, and it does not include nomegestrol and its esters.

2) The European patent only claims the continuous combined treatment; the estrogens and progestatives claimed are listed in tables present in the body of the text and summarised in the claims. There too, nomegestrol and its esters do not feature in the lists of progestatives that can be used. Now, nomegestrol acetate is characterised by a powerful progestational action, an absence of residual androgenic and estrogenic effects, and a powerful anti-estrogenic action which is manifested at the level of the endometrium by marked anti-mitotic activity and, consequently, a pronounced atrophying effect. Accordingly, it cannot be likened to the other progestatives and to think in terms of a dose correspondence relative to another progestative taken as reference cannot but be erroneous. Moreover, nomegestrol acetate is characterised by excellent tolerance; it has no effect on the lipids profile, the tolerance to glucides, the arterial pressure and the coagulation factors, even when used at doses higher than those described in the present patent application and in prolonged treatments (BASDEVANT et al., 1997). This aspect is very important because all therapists in common strive to use the treatment with least possible toxicity involving the lowest possible doses. In this respect, nomegestrol acetate differs from many derivatives of 19-nortestosterone cited in the PLUNKETT patents, which are progestatives characterised by androgenic and estrogenic effects which can have consequences at the level of the endometrium and which also have harmful metabolic effects.

For the same reasons as those mentioned above, none of the numerous publications that deal with the continuous combined treatment of the menopause can have a bearing on the present invention because none of these publications deals with an association of nomegestrol acetate with an estrogen. This for example applies to associations of estradiol and norethisterone acetate

(STADBERG et al., 1996; DOREN and SCHNEIDER, 1996; DOREN et al., 1997; EIKEN et al., 1997; PIEGSA et al., 1997; HART et al., 1998), estradiol and medrogestone (AFFINITO et al., 1998), estradiol and norgestrel (WOLFE and PLUNKETT, 1994), estradiol valerianate and chlormadinone acetate (RAUCH and TAUBERT, 1993), and conjugated equine estrogens with medroxyprogesterone acetate (REUBINOFF et al., 1995; WOLFE and HUFF, 1995; MIZUNUMA et al., 1997) or medrogestone (RECKER et al., 1999).

b) The fact that this estrogen-progestative association is different from the association previously patented by the Applicant.

In effect, French Patent No. 2.754.179 in the name of the Applicant claimed an association of estradiol and nomegestrol acetate for the combined replacement therapy of the menopause. The dose range claimed on the basis of previous experience with nomegestrol acetate in consecutive therapy was from 1.5 to 3.75 mg, preferably 2.5 mg. Now, clinical trials on a broader scale have shown that in an unexpected way, very much lower doses of nomegestrol acetate can induce endometrial atrophy with very good control of bleeding. This observation is important because it allows the nomegestrol acetate doses to be reduced still further, so that it can be used with still greater safety. The doses of Estradiol claimed in this patent ranged from 0,5 to 3 mg. The same doses of Estradiol are used but the ratio estrogen / progestative appears to be markedly altered 1:5 instead of 6:1.

c) Appropriate production method for the pharmaceutical forms

The invention concerns a production method with which the two active ingredients can be combined in one and the same pharmaceutical form.

The compositions according to the invention, based on nomegestrol acetate and free or esterified estradiol or conjugated equine estrogens, are administered either continuously or intermittently (from 21 to 28 days per month).

According to a particular embodiment of the invention, the compositions contain a quantity of

nomegestrol acetate ranging from 0.3 to 1.5 mg and a quantity of free or esterified estradiol or conjugated equine estrogens ranging from 0.3 to 3 mg. Preferably, the optimum formulations contain 0.625 to 1.25 mg of nomegestrol acetate associated with 0.5 to 1.5 mg of free estradiol or 1.5 to 2 mg of estradiol ester or 0.312 to 0.625 mg of conjugated equine estrogens, in each daily dose.

This mode of combined administration is indicated in menopausal women, whether the menopause is natural or the result of surgery; the estrogen-progestative combination is intended to compensate the functional disturbances induced by the menopausal estrogen deficiency, while maintaining endometrial atrophy and avoiding the appearance of deprivation bleeding in most of the women.

A further objective of the present invention is a process for obtaining new pharmaceutical compositions, which consists in mixing the active ingredients: nomegestrol acetate and free or esterified estradiol or conjugated equine estrogens, with one or more inert, non-toxic and pharmaceutically acceptable diluents or vehicles.

Among the excipients may be mentioned binding and dissolution-promoting agents, compaction agents, disintegration agents and slip-promoting agents.

The said mixture is compacted directly or in several stages to form tablets which can be protected on the surface, if desired, with a film, a coating, or by being made into dragees. The production of tablets by direct compaction makes possible the maximum reduction of the proportion of dilution agents, binding agents, disintegration agents and slip-promoting agents.

Soft gelatine capsules can be produced by mixing the active ingredients with an inert diluent and with a sliding agent.

The tablets contain, in particular, agents which dilute the mass such as lactose, sorbitol for direct compaction, as marketed under the name NEOSORB 60, Palatinite which is the registered trademark designating an equimolar mixture of isomer of [D]glucopyranosido-1,6-mannitol and

[D]glucopyranosido-1,6-glucitol crystallised with two water molecules, mannitol, sorbitol, or the lactose/PVP mixture marketed under the name Ludipress.

The compaction binding agents are generally microcrystalline celluloses such as those marketed under the name AVICEL PH 101 or AVICEL PH 102. Polyvinylpyrrolidone also plays an important part by facilitating the agglomeration of the powders and the compressibility of the mass. The polyvinylpyrrolidones used for this purpose have molecular weights between 10 000 and 30 000, such as Povidone, or Kollidon graded from 12 to 30.

The mixture also contains slip-gliding or anti-electrostatic agents which prevent the powder from agglomerating in the feed hoppers. In this connection the colloidal silicas marketed under the name AEROSIL, 100 or AEROSIL 200 may be mentioned.

The mixture also contains disintegration agents which make for disintegration or crumbling in accordance with pharmaceutical standards. As useful disintegration agents it may be mentioned the cross-linked vinylpyrrolidone polymers such as those marketed under the names Polyplasdone or Polyclar AT, carboxymethyl starches such as those marketed under the names Amijel or Explotab, or cross-linked carboxymethyl celluloses such as the compound sold under the name AC-DI-SOL.

In addition, the preparation contains lubricant agents which facilitate compaction and the ejection of the tablet from the tableting machines. As lubricants it may be mentioned glycerol palmitostearate as sold under the name Precirol, magnesium stearate, stearic acid or talc.

After compaction the tablets can be coated to improve their storage properties or to facilitate swallowing.

The coating agents are either cellulosic, such as cellulose phthalate (Sepifilm, Pharmacoat), or polyvinylic of the OPADRY PVA or Sepifilm ECL type, or saccharosic such as the sugar for coating of the Sepisperse DR, AS, AP or K types (coloured).

The tablets, whether coated or not, can in addition be coloured at the surface or throughout, with

mineral, vegetable or synthetic dyes (for example lacquer with quinoline-yellow, or E 104 or iron oxides).
The proportions of the various constituents vary according to the nature of the tablet to be made.

The content of active ingredients can range from 0.3 to 1.5 mg for the nomegestrol acetate and from 0.3 to 3 mg for the free or esterified estradiol or for the conjugated equine estrogens. The dilution agents range from 20 to 75% of the total mass, the gliding agents from 0.1 to 2% of the total mass, the compaction binding agents range from 2 to 20%, the polyvinylpyrrolidone from 0.5 to 15%, the disintegration agents range from 2 to 5.5% for cross-linked polyvinylpyrrolidone or carboxymethyl starch, and from 2.0 to 3.0% for croscarmellose.

The quantities of lubrication agents vary from 0.1 to 3.0%, depending on the type of agent.

The compositions according to the invention are intended to be administered once per day. However, depending on the therapeutic needs, the administration may be divided (twice daily) or, on the contrary repeated (two tablets per day).

The following examples illustrate the invention without limiting it in any way.

EXAMPLE 1 : Examples of formulations

The association of nomegestrol acetate and estradiol is presented in the form of plain or film-coated tablets.

The mixture of ingredients can either be compacted directly, or a preliminary estradiol mixture can be made into which the nomegestrol acetate and the other excipients are then incorporated in dry form. The preliminary estradiol mixture is made by dissolving the estradiol in an alcoholic solution of microcrystalline cellulose, PVP and lactose, drying it, and then grinding and calibrating it. This process is advantageous because tablets made from a preliminary estradiol mix have an estradiol dissolution profile which is appreciably better compared with tablets made by direct compaction.

The final mixture can contain from 1.5 to 5% of estradiol in povidone (5 to 25%), microcrystalline cellulose (5 to 15%) and lactose (enough to make up to 100%). It can be advantageous to introduce an anti-oxidant agent such as alpha-tocopherol or ascorbic acid during the preparation of the preliminary mix.

As an example, the following preliminary mix can be mentioned:

FORMULATIONS	in mg/one tablet	in %
Estradiol	1.50	1.82
PVP K25	13.50	16.36
Lactose 8195	60.00	72.73
Microcrystalline cellulose	7.50	9.09
TOTAL DRY MIX	**82.50**	**100.00**

This preliminary mix is introduced into the final mixture to obtain a tablet by direct compaction.

The finished tablets, uncoated, generally weigh 60 to 200 mg and have the following overall formulation:

FORMULATIONS OF THE UNCOATED TABLETS

Composition

		in mg per tablet
-	Estradiol (pre-mix, quantity sufficient for)	**0.3 to 3.0**
-	Nomegestrol acetate	**0.300 to 1.500**
-	Colloidal silica	0.400 to 2.000
-	Crospovidone	2.500 to 4.000
-	Lactose	60.000 to 80.000
-	Cellulose	10.000 to 25.000
-	Stearic acid	0.900 to 3.000
-	Talc	0.450 to 1.500

As examples, tablets can be mentioned which weigh 185 mg and have the following formulas:

Example of the formulation (UF = unitary formulation) of 185 mg tablets

FORMULATION	**UF mg per 1 tablet of 185 mg**	**UF %**
Estradiol	1.500	0.811
Nomegestrol acetate	**0.625**	0.338
Lactose	131.790	71.238
Cellulose (Avicel PH 101)	27.810	15.032
Povidone (K25)	13.500	7.297
Precirol (AT05)	2.780	1.503
Colloidal silica (Aerosil 200)	1.000	0.540
Crospovidone (Polyplasdone XL)	6.000	3.243
TOTAL	**185.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 185 mg tablets

FORMULATION	UF mg per 1 tablet of 185 mg	UF %
Estradiol	0.500	0.270
Nomegestrol acetate	**0.625**	0.339
Lactose	136.787	73.934
Cellulose (Avicel PH 101)	32.813	17.736
Povidone (K25)	4.500	2.432
Precirol (AT05)	2.775	1.500
Colloidal silica (Aerosil 200)	1.000	0.540
Crospovidone (Polyplasdone XL)	6.000	3.243
TOTAL	**185.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 120 mg tablets

FORMULATION	UF mg per 1 tablet of 120 mg	UF %
Estradiol	1.500	1.250
Nomegestrol acetate	**1.250**	1.042
Lactose	84.000	70.000
Cellulose (Avicel PH 101)	11.250	9.375
Povidone (K25)	13.500	11.250
Colloidal silica (Aerosil 200)	1.000	0.833
Crospovidone (Polyplasdone XL)	3.000	2.500
Magnesium stearate	1.000	0.833
Talc	1.000	0.833
Stearic acid AC/50VG	2.500	2.083
TOTAL	**120.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 120 mg tablets

FORMULATION	UF mg per 1 tablet of 120 mg	UF %
Estradiol	0.500	0.417
Nomegestrol acetate	**0.625**	**0.521**
Lactose	89.000	74.167
Cellulose (Avicel PH 101)	16.875	14.062
Povidone (K25)	4.500	3.750
Colloidal silica (Aerosil 200)	1.000	0.833
Crospovidone (Polyplasdone XL)	3.000	2.500
Magnesium stearate	1.000	0.833
Talc	1.000	0.833
Stearic acid AC/50VG	2.500	2.083
TOTAL	**120.00**	**100.000**

Example of the formulation (UF = unitary formulation) of 80 mg tablets

FORMULATION	UF mg per 1 tablet of 80 mg	UF %
Estradiol	0.500	0.625
Nomegestrol acetate	**0.625**	0.781
Kollidon 25	4.500	5.625
Lactose M	59.735	74.669
Cellulose (Avicel PH 101)	12.000	15.000
Crospovidone (Polyplasdone XL)	0.800	1.000
Talc	0.700	0.550
Colloidal silica (Aerosil 200)	0.440	0.550
Magnesium stearate	0.700	0.875
TOTAL	**80.000**	**100.000**

Example of the formulation (UF = unitary formulation) of 80 mg tablets

FORMULATION	UF mg per 1 tablet of 80 mg	UF %
Estradiol	1.000	1.250
Nomegestrol acetate	**1.250**	1.563
Kollidon 25	9.000	11.250
Lactose M	54.110	67.637
Cellulose (Avicel PH 101)	12.000	15.000
Crospovidone (Polyplasdone XL)	0.800	1.000
Talc	0.700	0.875
Colloidal silica (Aerosil 200)	0.440	0.550
Magnesium stearate	0.700	0.875
TOTAL	**80.000**	**100.000**

These tablets may be coated, for example with :

- film-forming agents based on polyvinyl alcohol of the type OPADRY PVA "moisture barrier" (polyvinyl alcohol, titanium dioxide, purified talc, lecithin, xanthan gum, pigments, lacquers),

or

- film-forming agents based on cellulose of the type SEPIFILM L.P. ([H.P.M.C. (hydroxypropylmethylcellulose)], microcrystalline cellulose, stearic acid, pigments, lacquers).

EXAMPLE II : Dissociation of the antimitotic and differentiating effects of nomegestrol acetate on endometrial cells

Menopausal women, whether naturally or as the result of surgery, were subjected to a sequential estrogen-progestative therapy. From Day 1 to Day 12 they received 30 **µg of** ethinyl estradiol and then, from Day 13 to Day 22, the same dose of ethinyl estradiol associated with different doses of nomegestrol acetate or chlormadinone acetate. The doses were as follows:

Nomegestrol acetate (mg):	0.1	0.25	0.5	1		2.5	5	and 10
Chlormadinone acetate (mg):	0.1		0.5	1	2		5	and 10

The number of women was between 2 and 11, depending on the group. There was then a therapeutic pause of 7 days followed by a second treatment cycle.

The parameters taken into account were as follows :

- the interval before periods commenced after the therapy had been interrupted, following the first and second treatment cycles;
- the histological appearance of the endometrium recovered in a biopsy carried out between Day 17 and Day 20 of the second cycle.

The results showed that :

- The interval before periods appeared is a function of the dose and is similar for both products. The dose required for no periods to appear before the end of the therapy is between 0.2 and 0.3 mg/day for both products (Table 1).

- The transformation of the endometrium into a secretory endometrium is total with both products from 1 mg/day upwards, but decreases at the highest doses (10 mg/day).

- The proliferation activity, expressed as the number of mitoses in the glandular cells, seems more strongly inhibited by nomegestrol acetate than by chlormadinone acetate. Mitosis no longer takes place in women treated with a dose equal to or higher than 0.5 mg/day of nomegestrol acetate, while mitosis is still evident with a daily dose of 1 mg/day of chlormadinone acetate (Table 2).

It can therefore be concluded that at the endometrial level, nomegestrol acetate and chlormadinone acetate are not comparable: the secretory transformation activity is comparable but nomegestrol acetate is characterised by a very marked antimitotic and antiproliferative action.

Table 1: Interval before the appearance of periods (days) after the therapy is discontinued

Progestative	Dose (mg/day)							
	0.1	0.25	0.5	1.0	2.0	2.5	5	10
Nomegestrol acetate	- 0.5 ± 1.5	- 0.5 ± 0.5	1.5 ± 0.5	2.7 ± 0.2		3.2 ± 0.2	4.3 ± 0.4	3.8 ± 0.8
Chlormadinone acetate	- 2.3 ± 0.5		2.0 ± 0.6	3.8 ± 0.3	3.8 ± 0.3		5.5 ± 1.5	5.5 ± 0.5

Table 2: Evaluation of the number of mitoses (% of section in which mitoses were present)

		Dose (mg/day)							
		0.1	0.25	0.5	1	2	2.5	5	10
Glands	Nomegestrol acetate	50	50	0	0	0	0	0	30
	Chlormadinone acetate	90			50	0		0	0

EXAMPLE III :

A trial was carried out to study the effects on the endometrium of the continuous combined association of an oral estradiol dose equivalent to 1.5 mg and various doses of nomegestrol acetate.

This consisted in the treatment for 6 consecutive months of 179 women who had been menopausal for at laest 3 years, with 1.5 mg per day of estradiol combined continuously with 4 different doses of nomegestrol acetate: 5 mg/day (n = 47); 2.5 mg/day (n = 42); 1.25 mg/day (n = 43) and 0.625 mg/day (n = 47).

The impact of these four associations on the endometrium was evaluated by recording the characteristics of genital bleeding, measuring the thickness of the endometrium by endovaginal echography before and at the end of the therapy, and by carrying out a biopsy of the endometrium before and at the end of the therapy.

The percentages of women who showed no genital bleeding at all throughout the therapy were respectively 42.5 - 58.1 - 52.4 and 68.1%, with the doses of 0.625 - 1.25 - 2.5 and 5 mg of nomegestrol acetate per day. The percentages observed are not statistically different between the groups, but the relation between the dose and the incidence of bleeding is significant.

The tables attached indicate, for each nomegestrol acetate dose, the results of the echographic examination and biopsy of the endometrium carried out at the end of the 6 months of treatment.

At the end of the therapy, the mean thickness of the endometrium is not different between the groups. The increase of the endometrial thickness under therapy is 0.39 mm on average with the smallest nomegestrol acetate dose. This thickening increases slightly as a function of dose, becoming 1.56 mm in the group of women who received 5 mg/day of the progestative, but the relation between the variation of thickness and the dose variation does not reach the threshold of statistical significance.

The biopsies of the endometrium examined at the end of the trial showed no proliferative or

hyperplasic appearance of the uterine mucosa. The highest percentage of secretory endometria was observed in the women who had received the highest progestative dose; it decreased progressively and in a statistically significant way with the dose. In contrast, the highest percentage of atrophic endometria was found at the lowest progestative dose and this decreased as the dose increased.

These results are unexpected in the sense that they show that low doses of nomegestrol acetate administered in continuous combination with an estrogen are capable of preventing the growth of the uterine mucosa and keeping it in an atrophic condition, whereas, in contrast to higher doses, they are insufficient to induce a secretory transformation of the endometrium.

Thus, this trial reveals a surprising decoupling of the anti-estrogenic effect of nomegestrol acetate from its progestational effect, when it is administered in continuous combination with estrogens.

The anti-estrogenic effect is preponderant since it is detectable when the progestative, administered continuously with an estrogen, is given at low doses. These doses are insufficient to bring about secretory transformations of the uterine mucosa. At higher doses and with the same therapeutic scheme, the secretory effect predominates, though without allowing excessive proliferation of the endometrium.

Table I - **Endometrial thickness after 6 months of continuous treatment with several combined associations based on estradiol (2 mg of estradiol valerate) and nomegestrol acetate (NOMAC) at various doses**

Doses of NOMAC (mg/day)	0.625 (n = 35)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 41)
Mean thickness at the end of the treatment (mm)	3.18 (1.65)	4.05 (3.75)	3.93 (2.10)	3.83 (2.72)
Mean thickness increase under the treatment (mm)	0.39 (1.67)	1.12 (3.67)	1.36 (1.54)	1.57 (2.39)

( ) = standard deviation

Table 2 - **Histological appearance of the endometrium after 6 month of continuous treatment with several combined associations containing estradiol (2 mg of estradiol valerate) and nomegestrol acetate (NOMAC) at various doses**

Doses of NOMAC (mg/day)	0.625 (n = 32)	1.25 (n = 33)	2.5 (n = 34)	5 (n = 40)
Absence of endometrium	5 (15.6)	10 (30.3)	3 (8.8)	3 (7.5)
Atrophic endometrium	19 (59.4)	10 (30.3)	8 (23.5)	3 (7.5)
Secretory endometrium	8 (25.0)	12 (36.4)	22 (64.7)	34 (85.0)
Polyps	0	1 (3.0)	1 (2.9)	0

( ) = percentage In no case was the endometrium proliferative or hyperplasic.

CLAIMS

1. Pharmaceutical hormone compositions characterised in that they are formed of a combined estrogen-progestative association intended for oral administration, and they make possible the simultaneous administration of an estrogenic compound at a dose ranging from 0.3 to 3 mg and a progestative compound derived from 19-norprogesterone at a dose ranging from 0.3 to 1.5 mg, in association or in admixture with one or more non-toxic, inert and pharmaceutically acceptable diluents.

2. Estrogen-progestative compositions according to Claim 1, in which the **estrogen is 17β-**estradiol, whether free or esterified, or conjugated equine estrogens.

3. Estrogen-progestative compositions according to Claim 1, in which the **estrogen is 17β-**estradiol.

4. Estrogen-progestative compositions according to Claim 1, in which the estrogen is an estradiol ester, such as estradiol valerate in particular.

5. Estrogen-progestative compositions according to Claim 1, in which the estrogen consists of conjugated equine estrogens.

6. Estrogen-progestative compositions according to Claim 1, in which the free or esterified estrogen or a conjugated equine estrogen is present in an amount ranging from 0.3 to 3 mg per unitary dose.

7. Estrogen-progestative compositions according to Claim 1, in which the estradiol is present in the free form preferably in an amount of 0.5 to 1.5 mg per unitary dose.

8. Estrogen-progestative compositions according to Claim 4, in which an estradiol ester is present, preferably in an amount of 1.5 to 2 mg per unitary dose.

9. Estrogen-progestative compositions according to Claim 1, in which the conjugated equine estrogen is present preferably in an amount of 0.312 to 0.625 mg per unitary dose.

10. Estrogen-progestative compositions according to Claim 1, in which the progestative is nomegestrol or one of its esters.

11. Estrogen-progestative compositions according to Claim 10, in which the progestative is nomegestrol acetate.

12. Estrogen-progestative compositions according to Claims 10 and 11, in which the nomegestrol acetate is present in an amount ranging from 0.3 to 1.5 mg per unitary dose.

13. Estrogen-progestative compositions according to Claims 10 to 12, in which the nomogestrol acetate is present in an amount between 0.625 and 1.25 mg per unitary dose.

14. A process for the preparation of new estrogen-progestative compositions according to Claim 1, in which the estrogenic active ingredient and the progestational active ingredient are admixed or combined with one or more inert, non-toxic and pharmaceutically acceptable diluents.

15. A method of using the estrogen-progestative mixture according to Claim 1, to produce a medicament intended for treating estrogen deficiencies in menopausal women in need thereof.

16. A method of using the estrogen-progestative mixture according to Claim 1, for producing a medicament intended to prevent osteoporosis and cardiovascular disorders in menopausal women in need thereof.

17. A method of using the estrogen-progestative mixture according to Claim 1, to produce a medicament intended for continuous or intermittent administration in need thereof.

GEI-073

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
JACQUES PARIS et al
Serial No.: 423,109
Filed: October 29, 1999
For: NEW HORMONAL...AND ITS USE

600 Third Avenue
New York N.Y. 10016
June 7, 2001

DECLARATION

Asst. Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants are submitting herewith a new declaration for the above application executed by the inventors. It is requested that the application now be entered into the national examination phase.

Respectfully submitted,
Bierman, Muserlian and Lucas

By: _____
Charles A. Muserlian #19,683
Attorney for Applicants
Tel.# (212) 661-8000

CAM:ds
Encl.: Declaration
Return receipt postcard

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (8-96)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☒ Declaration Submitted after Initial Filing

Attorney Docket Number	GEI-073
First Named Inventor	JACQUES PARIS et al
COMPLETE IF KNOWN	
Application Number	09/423,109
Filing Date	October 29, 1999
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

NEW HORMONAL COMPOSITION AND ITS USE

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☒ was filed on (MM/DD/YYYY) Oct. 25, 1999 as United States Application Number or PCT International Application Number PCT/FR99/02588 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56

☐ I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
PCT/FR99/02588	France	10/25/99	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

GEI-073

Please type a plus sign (+) inside this box → [+]

PTO/SB/01 (4-98)
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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian	19,683		
Jordan B. Bierman	18,629		
Donald C. Lucas	31,275		
Bierman, Muserlian and Lucas	18,818		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

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Address					
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Country	U.S.A.	Telephone	(212) 661-8000	Fax	(212) 661-8002

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	JACQUES	Middle Initial		Family Name	PARIS	Suffix e.g. Jr.	
Inventor's Signature	JACQUES PARIS					Date	05/07/01
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Post Office Address							
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City	Nice	State		Zip	06100	Country	France

☒ Additional inventors are being named on supplemental sheet(s) attached hereto

Please type a plus sign (+) inside this box → [+] GEI-073

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	JEAN-LOUIS	Middle Initial		Family Name	THOMAS	Suffix e.g. Jr.	
Inventor's Signature	JEAN LOUIS THOMAS				Date	05/10/01	
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Post Office Address							
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City	Charenton-Le-Pont	State		Zip	94220	Country	France

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature					Date		
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

DECLARATION AND POWER OF ATTORNEY

Each below-named inventor hereby declares and says that:

My residence, post office address and citizenship are as stated below beneath my name; I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the invention titled:

NEW CONTRACEPTIVE MEDICINAL PRODUCT AND METHOD FOR ITS PREPARATION

which is described and claimed in the attached application, or Serial No._____ _____ filed_____as amended to date; I have reviewed and understand the contents of the specification including the claims with all the above-mentioned amendments thereto, if any. I acknowledge my duty to disclose information of which I am aware which is material to the patentability of this application in accordance with 37 CFR 1.56; and, if the benefit of 35 U.S.C. 120 is claimed below, as to subject matter of the claims not disclosed in any prior U.S. application in accordance with 35 U.S.C. 112, I acknowledge my duty to disclose material information which became known to me between the filing date of said prior U.S. application and this application and is material to the patentability of this application as defined in 37 CFR 1.56; the benefit of 35 U.S.C. 119(e), or 120 is claimed for

SERIAL NO	FILED	STATUS

I claim the foreign priority benefits under 35 U.S.C. 119 of foreign application(s) for patent or inventor's certificate(s) filed less than 12 months prior to the filing of the application, or less than 12 months before the application(s) for which the above benefit of 35 U.S.C. 120 is claimed as follows:

COUNTRY	SERIAL NO.	FILING DATE

and I have identified any foreign application(s) for patent or inventor's certificate(s) having a filing date before the earliest of the application(s) for which priority is claimed, or the present application, as follows:

COUNTRY	SERIAL NO.	FILING DATE

BIERMAN, MUSERLIAN and LUCAS LLP, Customer No. 20311, Reg. No. 18,818; JORDAN B. BIERMAN, Reg. No. 18,629; CHARLES A. MUSERLIAN, Reg. No. 19,683; and DONALD C. LUCAS, Reg. No. 31,275; all of 600 Third Avenue, New York, New York 10016, Telephone (212) 661-8000, are hereby

appointed my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, with the understanding that they represent my assignee, if any.

It is declared by undersigned that all statements made herein of undersigned's own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S. Code 1001, and that such willful false statements may jeopardize the validity of this application or any other patent issuing thereon.

INVENTOR: SIGNATURE	DATE	RESIDENCE AND POST OFFICE ADDRESS
Signature PARIS Jacques	Date: 02 Nov 1999	31 avenue Cap de Croix Le Clos de Cimiez, Bât.E,Porte 1 06100 NICE FRY FRANCE
Name: PARIS Jacques	Citizen of: France	
Signature THOMAS Jean Louis	Date: 04 Nov 1999	16 rue Gabriel Peri 94220 CHARENTON-LE-PONT FRANCE FRX
Name: THOMAS Jean-Louis	Citizen of: France	
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